PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	04.03.2005
Applicant's or agent's file reference: SCB72471WO00	**REPLY DUE** within **2 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/002678	22.06.2004	26.06.2003

International Patent Classification (IPC) or both national classification and IPC
C07K5/08

Applicant
PEPHARM R&D LIMITED et al.

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1. This written opinion is the **second** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4.bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 26.10.2005

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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-46 as originally filed

Claims, Numbers

1-19 filed with the demand

Drawings, Sheets

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☒ the claims, Nos.: 20-29
   ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 4, 5, 19 (all partially)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 4,5,19 (all partially)

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	(no) 1-5, 7,8,19
Inventive step (IS)	Claims	(no) 6, 9-18
Industrial applicability (IA)	Claims	(no) 9-12 (see Sep. sheet)

2.

see separate sheet

novelty destroying for claims directed to the polypeptide per se.

2.2 Not all the claims specify a peptide "consisting of" the tripeptide YSV. Claim 5 refers to a pharmaceutical composition **comprising** the tripeptide YSV. Claim 6 refers again to a pharmaceutical composition, but comprising a polypeptide **consisting** of the tripeptide YSV. This juxtaposition of the two claims and their differing terminology suggests that the scope of Claim 5 extends to peptides **comprising** the tripeptide YSV.

D2 discloses the peptide YSVT and pharmaceutical compositions thereof for treating or preventing cancer, and as a food supplement.

This is considered to fall within the scope of Claim 5 due to the "comprising" language used and thus is novelty-destroying for this claim.

2.3 Claim 7 similarly refers to a composition **comprising** the tripeptide YSV. Although Claim 7 depends upon Claim 6, and is unclear in scope as a result, the disclosure of D2 is relevant to Claim 7 due to this wording.

2.4 Claim 8 relates to a method of making a pharmaceutical composition comprising mixing the tripeptide YSV with a pharmaceutical carrier. Claim 8 does not specify a polypeptide **consisting** of the tripeptide YSL; given the use elsewhere in the claims of the term "consisting", it is assumed that this absence is meaningful, and thus polypeptides **comprising** the tripeptide are encompassed.

As a result, the disclosure of D2 is novelty destroying for Claim 8.

3. Inventive step (Article 33(3) PCT)

3.1 D3 does not disclose any therapeutic applications of the YSV peptide synthesised, and thus is not considered to be relevant to the inventive step of claims including a therapeutic feature (ie, Claims 6, 9-19).

3.2 D1 may be considered as the closest prior art. D1 discloses the tripeptides YSL and YSF. These two tripeptides display the same activities as the presently-claimed YSV; modulation of the immune response, growth of different types of cancer etc.

relation to this wording used in Claim 5, this "comprising" languages appears to be broader than the "consisting" language. Thus, Claim 7 appears to be broader than Claim 6, which results in a lack of clarity. Claim 7 could be deleted.

4.4 Claim 19 refers to an "enhancement molecule", which molecule is defined as being one which enhances the therapeutic effectiveness of the tripeptide. This definition is a desideratum, and lacks meaning in the art as to what technical features are intended. As such, this claim lacks clarity

4.5 Industrial applicability

Claims 9-12 are directed to a **method of treatment of the human or animal body**.

For the assessment of Claims 9-12 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims (Rule 39 PCT).

Starting from D1, the problem to be solved may be formulated as provision of a further tripeptide which is useful in treatment of different types of cancer and as a nutritional supplement.

The solution to this problem as provided by the present claims, is to substitute the C-terminal residue of YSL for a valine residue. The skilled person, aware of the tripeptide YSL described in D1, and aware of the teaching in D1 whereby for peptides with non-polar or hydrophobic side chains it may be possible to substitute one side group for another without reducing the biological activity (see p. 56, lines 36-40), would consider at least conservative substitutions of the only non-polar or hydrophonic side chain residue in this peptide; the C-terminal leucine residue. The claimed peptide, YSV, is one such conservative substitution which does not reduce the biological activity. There is not a large number of possible conservative substitutions of leucine, thus, the selection of valine is not considered to represent a selection invention with a surprising technical effect.

Thus, the subject-matter of the present application does not appear to comprise an inventive step and therefore does not meet the requirements of Article 33(3) PCT.

4. Further remarks

4.1 Claims 1, 4, 6, 8, 9 and 13-19 all relate to the tripeptide YSV, without specifying that the amino acids in the tripeptide are all of the L-isomer. Thus, these claims encompass tripeptides containing one or more residues as D-isomers. However, the description only provides support and disclosure for the L-isomer form; there is neither disclosure of tripeptides comprising D-isomer residues, nor any evidence to suggest that they would show the same effect as an all L-isomer tripeptide (Rule 66.2(a)(v) and Rule 70.12(ii) PCT).

Thus, the independent claims should specify that the residues are all in the L-isomer form.

4.2 The claims as a whole lack clarity due to the presence of more than one independent claims directed to the same subject-matter. Claims 5 and 6 are both directed to a pharmaceutical composition comprising a tripeptide.

4.3 Claim 7 depends upon Claim 6, yet whereas Claim 6 refers to a polypeptide consisting of the tripeptide YSV, Claim 7 introduces "comprising" language. As discussed above in

Re Item V

1. The following documents are referred to in this communication:

D1: WO 03/006492 A
D2: WO 02/087507 A
D3: FURKA A, et al (2000), J. Comb. Chem. vol. 2, no. 3, pages 220-223

2. Novelty (Article 33(2) PCT)

2.1 The subject-matter of Claims 1-5, 7, 8 and 19 does not appear to be novel in view of the teaching of the cited prior art.

D3 discloses a synthesis method for oligomers, and exemplifies the method with a 125-member tripeptide library using Chiron crowns as solid support units and a simple manual device for sorting.

The present claims relate to an "isolated or purified peptide". The applicant has argued that D3 merely discloses a pool of a highly complex nature of which the tripeptide tyrosyl-seryl-valine (YSV) is among its components. Thus, the applicant is effectively indicating that D3 does not disclose the "isolated or purified" feature of the claimed peptide.

D3 is concerned with the production of combinatorial libraries, and provides an example in which "crowns" attached to a string are used as solid support units. Each crown is therefore a synthesis site, onto which the tripeptides are built. Each tripeptide is attached to a crown, and twenty-five such crowns are on any one string . D3 describes how the crowns were sorted in order to ensure formation of all possible structural combinations during the synthesis; sorting involves transferral of the crowns into slots of a tray and removal of the string. The implication of this method, in particular the sorting aspect, is that it suggests that the tripeptides are always distinct entities. In fact, it can be said that whilst the tripeptides are on the crowns, they cannot form a mixture. Thus, the YSV tripeptide of D3 is not merely one component of a complex pool; it is a distinct entity which is purified during the sorting.

In conclusion, the applicant's argument is not accepted, and D3 is considered to disclose an isolated or purified tripeptide with the sequence YSV (Table 3 position 20, string 4). This is

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